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Bronchiolitis obliterans syndrome (BOS) following heart-lung transplantation

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Abstract With the increasing number of successfully performed lung transplants and a longer follow up of patients, there is an interest in the analysis of long-term complications and their impact on patient survival. Heart-lung transplantation was performed in 157 patients with 126 patients surviving at least 6 months. Early death was mainly caused by bacterial and viral infection. Long-term patient survival was decisively influenced by obliterative bronchiolitis. With the new international definition of bronchiolitis obliterans syndrome (BOS) based on an irreversible decline of FEV1 from baseline values, it became possible to analyse the incidence of BOS and the impact on patient mortality in long-term survivors. FEV1 reached a peak value of 102 % predicted at a median of 219 days. In 106 of 126 patients (84 %), FEV1 showed no decline within the first year. A total of 60 patients (47.6 %) developed BOS grade 1 with progression to BOS grade 2 in 85 % of these patients. The incidence of BOS was 12.6 % at 1 year increasing to more than 50 % 5 years after transplantation. Patient mortality due to obliterative bronchiolitis increased from 1 % at 1 year to 18 % more than 5 years after transplantation. Almost all deaths (86 %; 32/37) more than 1 year after HLT were associated with bronchiolitis obliterans. In summary, bronchiolitis obliterans decisively contributes to long-term patient morbidity and mortality after heart-lung transplantation. Clinical and research efforts should be directed towards avoiding this important complication.

Key words Bronchiolitis obliterans syndrome · Lung transplantation

Introduction

Lung transplantation has become a therapeutic option for patients with end-stage lung diseases associated with a poor prognosis. Patient mortality following lung transplantation can be attributed to typical short-term and long-term complications. Short-term complications include primary organ failure, pleural bleeding, anastomotic stenosis or dehiscence, acute rejection and infection. Long-term survival and quality of life is mainly affected by obliterative bronchiolitis. As early as 1984, obliterative bronchiolitis was described in a considerable number of heart-lung transplant recipients [1]. Obliterative bronchiolitis was defined as an irreversible severe air flow obstruction as measured by lung function in the absence of acute rejection or infection. Autopsy in patients affected by obliterative bronchiolitis showed bronchiectasis, obliteration of the small airways, interstitial and pleural fibrosis, and accelerated arterial and venous arteriosclerosis. Early reports found obliterative bronchiolitis in around 50 % of patients surviving the first year after surgery [2]. One of the problems associated with earlier reports is that no universally accepted definition of obliterative bronchiolitis was available,

and, therefore, the definition of the time to develop this complication was not standard between transplant centres. The working formulation for the standardisation of nomenclature of bronchiolitis obliterans syndrome (BOS) as defined by an international working group has recently established a clinical definition [3]. The definition of BOS using lung volumes is very helpful because obliterative bronchiolitis can not often be found in transbronchial biopsies and the efficacy of biopsies in the diagnosis varies between centres [4–6]. After heart-lung transplantation, lung volumes return to the predicted values of the recipient [7] in contrast to single lung transplantation. However, using the decline in FEV1 from baseline values for the definition of BOS, it is now possible to classify patients according to the international grading system and to compare the incidence of BOS between different centres using different immunosuppressive regimens in single, bilateral and heart-lung transplant recipients.

With the increasing number of patients undergoing successful heart-lung transplantation and with a longer follow up, we could study the incidence of BOS up to more than 5 years after transplantation and the impact on patient mortality.

Patients and methods

Patients

Between 1984 and 31 December 1993, 157 patients underwent heart-lung transplantation. The underlying diseases were: 56 cystic fibrosis, 34 Eisenmenger's syndrome, 18 primary pulmonary hypertension, 16 emphysema, 10 bronchiectasis, 5 sarcoidosis and 18 others.

Immunosuppression

Equine anti-lymphocyte globulin (ATG) was given for the first 3 days. Intraoperatively, 1000 mg of methylprednisolone was given followed by three doses of 125 mg during the first postoperative day. Cyclosporin A was given from the first day onwards to achieve whole blood levels between 300 and 600 ng/ml for the first few months and the daily azothioprine dose consisted of 2 mg/kg. Acute rejection was treated with 500–1000 mg methylprednisolone followed by oral prednisone (1 mg/kg) decreasing the dose over 10 days. In patients with repeated rejection episodes, triple therapy with cyclosporin A, azathioprine and prednisone was maintained. Steroids were only withdrawn if lung function remained stable and if there were no signs of rejection in the following 3 months.

Lung function

Routine lung function measurements included FEV1, vital capacity, total lung capacity and diffusion capacity, and were taken at 1, 3, 6, 9 and 12 months after transplantation and thereafter at 3–6 month intervals. In addition, measurements were taken if patients developed symptoms or signs of pulmonary rejection or infection or had radiological abnormalities. Patients performed daily home spirometry and returned to hospital for full lung function tests if a decline of at least 5 % was observed. If a deterioration in lung function was confirmed, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy was performed to detect rejection or infection.

Bronchiolitis obliterans syndrome (BOS)

BOS was defined as an irreversible decline in FEV1 of at least 20 % of the individual baseline values and graded according to the recommendations of an international study group [3]. Baseline was determined as the maximum FEV1, taken at least 30 days apart in the first year after transplantation. Acute rejection and infection were excluded by bronchoalveolar lavage and transbronchial biopsy. Irreversible decline of FEV1 was graded as follows: BOS grade 0, FEV1 at least 80 % of baseline; BOS grade 1, FEV1 between 66 % and 80 % of baseline; BOS grade 2, FEV1 between 51 % and 65 % of baseline; BOS grade 3, FEV1 between 0 % and 50 % of baseline.

Statistics

Kaplan-Meier methods were used to describe the actuarial survival time and time to development of BOS grades.

Results

Between 1984 and December 1993, 157 patients underwent heart-lung transplantation. Overall patient mortality dropped from 9 % (14 of 157) in the first postoperative month to 4 % (6 of 143) in the second and 4 % (5 of 137) in the third. Infection was the most common cause of death, occurring in 18 of the 31 patients (58 %) who died within the first 6 months after surgery. Eleven patients died with bacterial infection including empyema (3) and pneumonia (3). There were 5 cases of fatal CMV pneumonitis, 4 of them involved seronegative recipients of organs from seropositive donors. Three of these occurred before ganciclovir treatment for CMV became available. Non-infective causes of death include primary graft failure (4), tracheal dehiscence (2), cerebrovascular event (1), gastrointestinal bleeding (1) and lymphoproliferative disorder (2). Postoperative bleeding was a frequent complication requiring reoperation in 34 (22 %) patients. There were no deaths as a result of pleural bleeding but reoperation was often associated with secondary complications, especially infection. Acute rejection was very common, occurring in 141 of 157 patients (90 %) within 3 months of transplantation. Rejection was successfully treated in all but 1 patient. One patient died in the second postoperative month with severe graft versus host disease.

Patients surviving at least 6 months were included for analysis of BOS because they were at risk of developing this complication. From these 126 patients, 5 died within the second 6 months after surgery reflecting the consid-

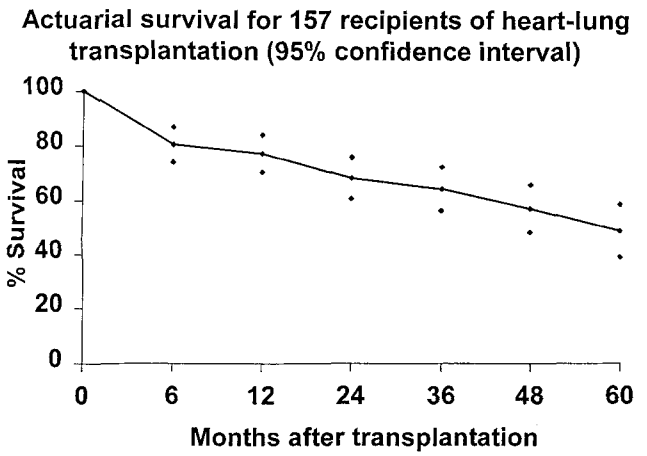

Fig. 1 Actuarial survival for 157 recipients of heart-lung transplantation

erable drop in mortality in the second half of the first year. Only 1 of 36 patients who died within the first year had obliterative bronchiolitis as an underlying complication. Graft survival, which was similar to patient survival, is shown on Fig. 1.

After surgery, FEV1 steadily increased and reached a peak value of 102 % (SD 22.6 %) predicted for the 126 heart-lung transplant recipients surviving at least 6 months. Peak FEV1 was reached at a median of 219 days (interquartile range 140–303 days) after transplantation. FEV1 above 80 % predicted was achieved by 105 patients at a median of 46 days (interquartile range 24–125 days). Using the grading system for BOS as described above, a total of 60 patients (47.6 %) developed BOS grade 1, 51 patients BOS grade 2 and 36 patients BOS grade 3. Table 1 shows the worst BOS grade achieved by patients who survived 6 months, for each year after transplantation. Between 7 and 12 months after surgery, 106 (84 %) patients showed no deterioration of lung function, reflecting an incidence of BOS of 13 %. The number of patients free of any functional deterioration had declined from 84 % at the end of the first year to 61 % at 3 years and 45 % at 5 years. At the final measurement before analysis, 39 % of patients transplanted longer than 5 years still had normal lung volumes. On the other hand, the number of patients developing BOS increased steadily each year to 55 % at 5 years. At the time of reporting, only 15 % (9/60) of patients with BOS grade 1 have failed to develop BOS grade 2 indicating a rapid deterioration of lung volumes in patients with BOS. Median survival time from the time of development of BOS grade 1 was 948 days (interquartile range 306–2039). The percentage of patients who died with obliterative bronchiolitis increased from 1 % (1/126) at 1 year to 18 % (6/33) more than 5 years after transplantation. More than 1 year after transplantation, death was associated with bronchiolitis obliterans in 86 % of patients (32/37). A total of 27 of 60 patients with BOS (45 %) were alive at a median of 2.6 years after the diagnosis of BOS grade 1. There were 9 deaths more than 6 months after transplantation which were not associated with obliterative bronchiolitis (cerebrovascular accident; malignancy; graft versus host disease; renal failure complicated by infection; aeroplane accident; drug overdose; bronchial stenosis).

In summary, almost all patients surviving 6 months achieved predicted lung volumes within the first year after transplantation. Afterwards, the percentage of patients developing BOS steadily increased over the years. Deaths occurring more than 6 months after transplantation are mainly influenced by the occurrence of bronchiolitis obliterans.

Discussion

Early mortality following heart-lung transplantation is mainly due to infection whereas long-term survival is decisively influenced by bronchiolitis obliterans. The new definition of BOS allows the comparison of the incidence of obliterative bronchiolitis between different centres. Given the importance of this long-term complication, much effort should be directed to the prevention of obliterative bronchiolitis.

Table 1 Patients surviving at least 6 months after heart-lung transplantation broken down by the worst grade of bronchiolitis obliterans syndrome *(BOS)* observed in each period (*OB* obliterative bronchiolitis)

BOS grade	Months after transplantation					
	7–12 *n* (%)	13–24 *n* (%)	25–36 *n* (%)	37–48 *n* (%)	49–60 *n* (%)	> 60 *n* (%)
0	106 (84)	80 (70)	57 (61)	36 (51)	21 (45)	13 (39)
I	1 (1)	8 (7)	8 (9)	8 (11)	4 (9)	1 (3)
II	9 (7)	5 (4)	7 (8)	6 (9)	6 (13)	4 (12)
III	5 (4)	9 (8)	16 (17)	13 (19)	10 (21)	9 (27)
Death with OB	1 (1)	10 (9)	4 (4)	6 (9)	6 (13)	6 (18)
Death without OB	4 (3)	3 (3)	1 (1)	1 (1)	0 (0)	0 (0)
Number alive at start of period	126 (100)	115 (100)	93 (100)	70 (100)	47 (100)	33 (100)

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